Synthetic Route Development for the Laboratory Preparation of Eupalinilide E.

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Public Summary:
The natural product eupalinilide E has the potential to address short supplies of hematopoietic stem and progenitor cells (HSPC) needed for the treatment of blood diseases and disorders. Eupalinilide E promotes the expansion of HSPC derived from cord blood (CB) and mobilized peripheral blood and inhibits differentiation. However, the world's supply of eupalinilide E was consumed in the preliminary studies validating its potential thereby precluding additional experiments. With no material available for additional testing the compound's mechanism of action and studies of its capability to translate from a basic finding to a clinically useful agent were not possible. To correct this we have developed the first laboratory preparation of the natural product and the synthetic route is capable of generating more than sufficient material to support the continued development in our laboratories as well as provide material for other research groups both academic and industrial.

Scientific Abstract:
Following the discovery that the guaianolide natural product eupalinilide E promotes the expansion of hematopoietic stem and progenitor cells; the development of a synthetic route to provide laboratory access to the natural product became a priority. Exploration of multiple synthetic routes yielded an approach that has permitted a scalable synthesis of the natural product. Two routes that failed to access eupalinilide E were triaged either as a result of providing an incorrect diastereomer or due to lack of synthetic efficiency. The successful strategy relied on late-stage allylic oxidations at two separate positions of the molecule, which significantly increased the breadth of reactions that could be used to this point. Subsequent to C-H bond oxidation, adaptations of existing chemical transformations were required to permit chemoselective reduction and oxidation reactions. These transformations included a modified Luche reduction and a selective homoallylic alcohol epoxidation.